

# ACIP Evidence-Based Recommendations Work Group Proposal

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## **ACIP and the GRADE approach**

- ❑ **ACIP adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in October 2010**
  - Quality of evidence for benefits and harms
  - Going from evidence to recommendations
- ❑ **Quality of evidence for benefits and harms is only one factor in developing a recommendation**
  - Other key factors include balance of benefits and harms, values, and health economic data
  - ACIP Charter states, “shall include consideration of disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, economic analyses and implementation issues.”

# The Role of Evidence Quality in Making a Recommendation

- “The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach clearly separates the certainty of evidence from the strength of recommendation. This separation allows decision-making based on lower levels of evidence. For example, despite low certainty evidence (derived from case series) regarding the association between aspirin and Reye’s syndrome in febrile children, a strong recommendation for using acetaminophen over aspirin is possible. GRADE literature also describes five paradigmatic situations in which a strong recommendation can be made based on low quality evidence”

From: Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. BMJ Evidence-Based Medicine Published Online First: 02 February 2018. doi: 10.1136/bmjebm-2017-110853

# Evidence to Decision (EtD) Frameworks

- ❑ EtD frameworks were developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group\*
- ❑ Frameworks are intended to help panels:
  - structure discussion and identify reasons for disagreements,
  - be more systematic and explicit about the judgments that they make, the evidence used to inform each of those judgments, additional considerations, and the basis for their recommendations or decisions
  - make the process and basis for decisions structured and transparent
- ❑ Frameworks assist users of recommendations by enabling them to understand the judgments made by the panel and the evidence supporting those judgments

*\*GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction*

*BMJ 2016; 353 doi: <https://doi.org/10.1136/bmj.i2016> (Published 28 June 2016)*

## **EtD Framework Structure**

- ❑ **EtD frameworks include three sections that reflect the main steps in going from evidence to a decision:**
  - formulating the question
  - making an assessment of the evidence
  - drawing conclusions
- ❑ **A key feature of EtD frameworks is that they are layered - presenting key messages in the top layer with links to more detailed information**
  - include concise summaries of the most important evidence for each criterion, summarized in a table or a paragraph of text
  - from the framework, it is possible to link to information that is more detailed – e.g., an evidence profile

## EtD Framework Content

- ❑ The 3 content areas are presented in the framework as:
  - **Background (formulating the question):**
    - Details of the question and a brief summary of information to understand the question & why recommendation is needed
  - **Criteria (assessment/communication of evidence):**
    - Criteria (factors that should be considered) for making the decision
    - Judgments that must be made in relation to each criterion
    - Evidence to inform each of those judgments
    - Additional considerations that inform or justify each judgment
  - **Conclusions** that the panel must reach, based on the judgments made for all of the criteria

# ACIP Evidence to Recommendation (EtR) Framework Development

- ❑ **Additional structure and clarity for the full spectrum of criteria evaluated during formulation of recommendations**
  - Factors have always been considered, but process not structured
  - Refine methods for the incorporation of additional factors that contribute to decision-making as well as GRADE evidence profiles
- ❑ **Evidence to Recommendation (EtR) framework**
  - Adapting the framework to best fit public health recommendations for vaccines
  - Piloted by Mumps and Zoster Oct meeting
  - Living document
  - Guidance document provides additional detail on development and use of the framework

# Proposed EtR Framework Criteria

## ❑ Statement of Problem

- Public health importance
- Burden of disease

## ❑ Benefits and Harms

- Balance of desirable and undesirable effects
- Certainty in evidence (evidence profiles)

## ❑ Values and Preferences of target population

## ❑ Acceptability to stakeholders

## ❑ Resource Use

- Health Economic Analyses

## ❑ Feasibility

- Implementation considerations

# EtR Framework Criteria

## ❑ For each of these Criteria the following are provided:

### ▪ **Judgments**

- For initial framework, draft judgements prepared by the WG that become final after review/modification by the full committee

### ▪ **Evidence to inform each judgment**

- May be research evidence or obtained from routine data collection
- If no peer-reviewed body of evidence is available, this should be simply stated and any additional information used to inform the judgment indicated
  - Intent is to be transparent about the information that was used to make the judgment, not to imply the need for the development of evidence when it is not available
- May include links to more detailed summaries of the evidence

### ▪ **Additional considerations that inform or justify each judgement**

- Can include other data, assumptions, and/or logic used to make a judgment
- Different judgments for one or more subgroups
- Dissenting views of panel members or minority opinions
- Interpretations of the evidence

## Proposed ACIP EtR Framework: Question, Background, and Problem

**Question:** Overarching policy question to be answered by the guideline panel (ACIP) using the Evidence to Recommendations (EtR) framework.

**Population:** Target population for vaccine (e.g., age range, sex, immune status, pregnancy)

**Intervention:** Vaccination (if applicable, dosage and schedule)

**Comparison(s):** No Vaccination/Placebo/Control/Standard care/An existing vaccine/Other prevention options

**Outcome:** Outcome(s) associated with vaccination (e.g., prevention outcomes or adverse effects)

**Background:** The addressed PICO question should be described in detail, and important background information for understanding the question and why a recommendation or decision is needed should be briefly provided.

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
		<i>No</i> <i>Probably no</i> <i>Uncertain</i> <i>Probably yes</i> <i>Yes</i> <i>Varies</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
PROBLEM	Is the problem of public health importance?			

# Proposed ACIP EtR Framework: Benefits & Harms

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS	How substantial are the desirable anticipated effects?	<i>Trivial</i> <i>Small</i> <i>Moderate</i> <i>Large</i> <i>Don't know</i> <i>Varies</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	How substantial are the undesirable anticipated effects?	<i>Trivial</i> <i>Small</i> <i>Moderate</i> <i>Large</i> <i>Don't know</i> <i>Varies</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	Do the desirable effects outweigh the undesirable effects?	<i>Favors intervention</i> <i>Favors comparison</i> <i>Favors both</i> <i>Favors neither</i> <i>Unclear</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	What is the overall certainty of this evidence for the critical outcomes?	<p>Effectiveness of the intervention</p> <i>No included studies</i> 4 <i>Very low</i> 3 <i>Low</i> 2 <i>Moderate</i> 1 <i>High</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
		<p>Safety of the intervention</p> <i>No included studies</i> 4 <i>Very low</i> 3 <i>Low</i> 2 <i>Moderate</i> 1 <i>High</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		

## Proposed ACIP EtR Framework: Values

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
VALUES	Does the target population feel that the desirable effects are large relative to undesirable effects?	<div> <i>No</i>  <input type="checkbox"/> </div> <div> <i>Probably no</i>  <input type="checkbox"/> </div> <div> <i>Uncertain</i>  <input type="checkbox"/> </div> <div> <i>Probably yes</i>  <input type="checkbox"/> </div> <div> <i>Yes</i>  <input type="checkbox"/> </div> <div> <i>Varies</i>  <input type="checkbox"/> </div>		
	Is there important uncertainty about or variability in how much people value the main outcomes?	<div> <i>Important uncertainty or variability</i>  <input type="checkbox"/> </div> <div> <i>Possibly important uncertainty or variability</i>  <input type="checkbox"/> </div> <div> <i>Probably no important uncertainty or variability</i>  <input type="checkbox"/> </div> <div> <i>No important uncertainty or variability</i>  <input type="checkbox"/> </div> <div> <i>No known undesirable outcomes</i>  <input type="checkbox"/> </div>		

# Proposed ACIP EtR Framework: Acceptability, Resource Use and Implementation

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	<div> <div>No</div> <div>Probably no</div> <div>Uncertain</div> <div>Probably yes</div> <div>Yes</div> <div>Varies</div> </div> <div> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </div>		
RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	<div> <div>No</div> <div>Probably no</div> <div>Uncertain</div> <div>Probably yes</div> <div>Yes</div> </div> <div> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </div>		
FEASIBILITY	Is the intervention feasible to implement?	<div> <div>No</div> <div>Probably no</div> <div>Uncertain</div> <div>Probably yes</div> <div>Yes</div> <div>Varies</div> </div> <div> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </div>		

# EtR Framework Conclusions

- ❑ **Conclusions should be based on the judgments made for all of the criteria and should specify:**
  - A summary of the judgements made for all criteria and implications for the decision
  - The type of decision or recommendation (e.g. Routine recommendation, individual recommendation, or not recommended)
  - The recommendation in concise, clear and actionable text
- ❑ **May include:**
  - Any subgroup considerations that the panel took into account when making a decision
  - Key implementation considerations (in addition to any that are specified in the recommendation), including strategies to address any concerns about the acceptability and feasibility of the intervention
  - Draft conclusions suggested by the WG who have prepared the framework

Adapted from DECIDE materials at <http://www.decide-collaboration.eu/evidence-decision-etd-framework>

# Proposed ACIP EtR Framework: Recommendation and Additional Considerations

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings <input type="checkbox"/>	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings <input type="checkbox"/>	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i> <input type="checkbox"/>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings <input type="checkbox"/>	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings <input type="checkbox"/>	There is insufficient evidence to determine the balance of consequences <input type="checkbox"/>
<p>Is there sufficient information to move forward with a recommendation?</p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>						
Type of recommendation	We do not recommend the intervention <input type="checkbox"/>		We recommend the intervention for individuals based on clinical decision-making <input type="checkbox"/>		We recommend the intervention <input type="checkbox"/>	
Recommendation (text)	Please provide the draft recommendations proposed to ACIP.					
Additional considerations (optional)	Please outline any significant additional considerations (e.g., aspects related to implementation, monitoring and evaluation, research priorities, etc.).					

## Type of Recommendation

- ❑ **Draft includes 3 types of recommendation**
  - “We do not recommend the Intervention”
  - “We recommend the intervention for individuals based on clinical decision-making”
  - “We recommend the intervention”
- ❑ **These types of recommendation will replace former “Category A” and “Category B” labeling of recommendations**

## Use of the ACIP EtR Framework

- ❑ **This is a proposed update to the current ACIP evidence-based recommendation process consistent with expansion of GRADE methodology guidance**
  - Precise language subject to continued improvement
  - Guidance will be updated as experience is gained
  - Additional supporting documents being developed
- ❑ **Previous recommendations will not be retroactively put into the EtR format but the framework will be used when recommendations are periodically updated**
- ❑ **Completed EtR frameworks will be published online**

# Evidence-Based Recommendations

## Work Group Members

### ACIP Members

Grace Lee (Chair)

Paul Hunter

### Liaison Representatives

AAP – Sean O’Leary

AAFP – Margot Savoy

ACP – Amir Qaseem

FDA – Roshan Ramanathan

NACI – Nadine Sicard and Shainoor Ismail

SHEA – David Weber

### Previous ACIP members

Arthur Reingold

Jon Temte

Doug Campos-Outcalt

Lorry Rubin

### CDC Contributors

EBRWG Lead - Wendy Carr (NCIRD)

ACIP Work Group leads - Tamara Pilishvili and Kathleen Dooling

Immunization Services Division - Carolyn Bridges and Megan Lindley

### Consultants

US GRADE Network - Rebecca Morgan

SAGE - Charles Wiysonge and Melanie Marti

Robert Koch Institute STIKO - Thomas Harder  
IDSA - Valéry Lavergne

Ned Calonge

## Vote

- ❑ **The EBRWG proposes that an Evidence to Recommendation framework be adopted and used by ACIP to support decision making**
  - Note: The terminology is NOT being voted on as it will likely evolve over time
  - Enhancements may be made to the framework in the future

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	INTREPRETATION OF EVIDENCE
PROBLEM	Is the problem a public health priority?	No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input type="checkbox"/> Probably Yes <input type="checkbox"/> Yes <input checked="" type="checkbox"/> Varies <input type="checkbox"/>	<p>Annual rate ~4 HZ cases per 1000 population (1 million cases annually)<sup>1,2</sup></p> <p>Incidence increases with age, ranging from &lt;1 case/1000 children to &gt;15 cases/1000 population 80 years and older<sup>2,3</sup></p> <p>The incidence among people 60 years of age and older is about 10 cases per 1,000 U.S. population annually<sup>1,2</sup></p> <p>In a study using administrative data, the annualized incidence of herpes zoster was 4.6, 6.9, 9.5, and 10.9 per 1000 people aged 50–59, 60–69, 70–79, and 80 years, respectively<sup>4</sup></p> <p>Risk of herpes zoster increases with age, and among persons who experience herpes zoster, older persons are more likely to also experience PHN<sup>4</sup>, non-pain complications<sup>4</sup>, hospitalizations<sup>5</sup>, and interference with activities of daily living<sup>6</sup></p> <p>For adults 50 years and older with HZ, 10-18% will go on to develop PHN. Incidence of PHN increases significantly with age<sup>7</sup></p> <p>For adults 50-59 years old with HZ, , an estimated 5-8% will go on to develop PHN<sup>8,9</sup></p> <p>ZVL, the current licensed and recommended herpes zoster vaccine, is 51% and 67% effective in preventing herpes zoster and PHN, respectively, among adults aged ≥60</p>	<p>Burden of herpes zoster increases with age, with steep increases occurring after age 50 years</p> <p>Although incidence is lower in 50-59 year olds compared to those over 60 yrs, ~21% of all HZ episodes occur in this age group annually. However, 50-59 year olds are less likely to experience complications due to herpes zoster compared to elderly adults.</p> <p>Complications from herpes zoster, including PHN and ocular complications, can be severe and debilitating. Likelihood of complications increases significantly with age.</p> <p>PHN and pain-associated with zoster, can have a significant negative impact on quality of life can cause chronic fatigue, sleep disorders, social isolation, depression and anxiety, and can interfere with basic activities of daily living</p> <p>The current zoster vaccine is only 51% effective at preventing herpes zoster, leaving a substantial number of individuals who receive the vaccine still at risk for disease.</p>

<sup>1</sup> Jumaan et al., JID, 2005, 191:2002-7.

<sup>2</sup> Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9.

<sup>3</sup> Insinga et al., J Gen Intern Med. 2005, 20:748-53.

<sup>4</sup> Insinga et al., J Gen Intern Med. 2005, 20:748-53.

<sup>5</sup> Lin F, Hadler JL. J Infect Dis 2000;181:1897–905.

<sup>6</sup> Schmader KE, Johnson GR, Saddier P, et al. J Am Geriatr Soc 2010;58:1634–41.

<sup>7</sup> Johnson, RW, and McElhaney, J. Int J Clin Pract. 2009 Sep; 63(9): 1386–1391.

<sup>8</sup> Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9.

<sup>9</sup> Gauthier et al 2009, Epidemiol Infect. 2009; 137:38-47